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Pretreatment with divided doses of steroids strongly decreases side effects of OKT3

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Pretreatment with divided doses of steroids strongly decreases side effects of OKT3. The aim of this study was to attenuate side effects of OKT3 by variation of the time interval between administration of corticosteroids and OKT3 in renal allograft recipients. In view of a maximal lymphocytopenia at six hours following MPNS, we postulated a greater preventive action on side effects from administration of methylprednisolone (MPNS) at six hours preceding the first dose of OKT3 compared to administration immediately before. Two groups of renal transplant patients treated for acute rejection with 5 mg OKT3 were studied. Ten patients received 500 mg MPNS six hours and ten patients one hour before administration of OKT3. We measured clinical side effects, body temperature, TNF and IL-6. There were no differences between the two groups regarding clinical side effects and peak body temperatures. However, MPNS administered six hours before administration of OKT3 diminished TNF release; MPNS one hour before decreased IL-6 release. We studied an additional group of six patients receiving 250 mg MPNS six hours before, followed by 250 mg one hour before OKT3. This group experienced significantly less side effects and lower body temperature. In addition, IL-6 levels were significantly decreased. We conclude that two times 250 mg MPNS administered six hours and one hour before the first administration of OKT3 effectively attenuates adverse reactions following administration of OKT3.

OKT3, a murine monoclonal IgG2a antibody (mAb) directed against the TCR-CD3 complex on T lymphocytes, has proven its efficacy in the prevention and treatment of allograft rejection [1–4]. Expanded clinical application, such as in the treatment of autoimmune diseases, may next be considered. However, the first dose of this mAb is almost invariably followed by chills, fever, dyspnea, headaches and gastrointestinal symptoms [5]. Data in the literature show a relationship between these adverse reactions and the appearance of circulating cytokines, that is, TNF, IFN-γ, IL-2, IL-3 and IL-6 [6–11]. These cytokines are thought to be released due to activation of mononuclear cells. In addition, administration of OKT3 induces complement activation via the classical pathway. Both cytokine release and complement activation leads to activation of granulocytes and sequestration of these cells in the lungs, which may explain respiratory side effects [12]. To diminish adverse reactions, the manufacturer recommends the first administration of OKT3 to be preceded by an intravenous bolus of corticosteroids. Corticosteroids are known to abrogate both systemic reactions as well as peak levels of TNF and IFN-γ following administration of anti-CD3 mAb in mice [13, 14] and in humans [6, 9, 15, 16]. Several of these authors suggest that not only the administered dose of corticosteroids is important in preventing systemic side effects, but also the time interval in between the administration of steroids and the mAb [9, 13, 14, 15]. Gaston et al demonstrated a positive correlation between the absolute number of circulating $CD3^+$ and $CD4^+$ cells present before therapy and the degree of clinical side effects [10]. Corticosteroids induce lymphocytopenia with a nadir at six hours following administration [17–20]. We hypothesized that the best moment to administer OKT3 would be six hours following administration of steroids, when circulating T lymphocytes are maximally decreased. Since a time interval between MPNS and OKT3 of one hour was claimed as the most beneficial in the literature [9, 16], we have chosen this interval as the other alternative of our study.

Most studies on modulating adverse reactions of treatment with anti-CD3 mAb by corticosteroids have been performed in mice, which are known to be steroid sensitive [13, 14]. Data obtained from those studies cannot be simply extrapolated to humans, who are a corticosteroid-resistant species [21]. In the two studies performed in humans on modulating clinical side effects following OKT3, interpretation of the results was hampered by the concomitant effects of anesthesia [9, 16]. Moreover, only time intervals up to 60 minutes between the administration of MPNS and OKT3 were tested.

The aim of the present study was to modulate the clinical side effects complicating the first dose of OKT3 by variation of the time interval between administration of MPNS and OKT3. Three different groups of renal transplant patients, treated with 5 mg OKT3 daily for ten consecutive days for acute cellular rejection were studied. One group received 500 mg MPNS six hours preceding administration of the first dose of OKT3, one group received 500 mg MPNS one hour prior to the first dose of OKT3 and one group received the same amount of MPNS but now divided in two doses of 250 mg, given six hours and one hour prior to administration of OKT3.

In addition to monitoring of clinical side effects, lymphocyte numbers were followed in time and plasma TNF, and IL-6 levels were determined at frequent intervals.

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Methods

Patients

Informed consent was obtained from all patients.

All patients were renal allograft recipients treated for acute cellular rejection. The diagnosis of acute rejection was made on clinical grounds and was histologically proven. Basic immunosuppressive therapy consisted of cyclosporine in a dosage based on serum trough levels and prednisolone 10 mg per day. First, lymphocyte counts following 500 mg MPNS were measured in five patients treated with a six day course of MPNS once a day. These patients experienced a second rejection, the former being treated with OKT3 at least four weeks before. Patients included in the actual study were all treated with a ten day course of OKT3, 5 mg once a day intravenously for their first rejection. Before administration of OKT3, overhydration was excluded by physical examination and a chest X-ray. Three different groups of patients were studied: 10 patients (6 male, 4 female; mean age 47 years, range 29 to 62 years) received 500 mg MPNS six hours prior to administration of OKT3 (−6 hr group), 10 patients (7 male, 3 female; mean age 47 years, range 37 to 65 years) received 500 mg MPNS one hour prior to administration of OKT3 (−1 hr group) and six patients (4 male, 2 female; mean age 46 years, range 38 to 58 years) received two times 250 mg MPNS at six hours and at one hour before administration of OKT3 respectively (−6/−1 hr group). MPNS was given as an infusion during 20 minutes and OKT3 was administered as a bolus injection. As is common in our department, all patients were also given 25 mg promethazine orally one hour before OKT3 administration.

Clinical parameters

Body temperature was measured orally prior to the first administration of OKT3 and 2, 4, 8, 12, 24, 36, and 48 hours afterwards.

Side effects were assessed in the following way: each patient was observed and questioned for the presence of (1) chills, (2) fever > 38.5, (3) dyspnoea, (4) vomiting or nausea (5) diarrhea, and (6) headache in the time intervals ranging from 0 to 3 hours, 3 to 6 hours, 6 to 12 hours, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours after the administration of OKT3. Each positive symptom, when present during a certain time interval, was graded one point. In this way, the maximum side effect score in a given time interval was 6.

Blood pressure was taken manually, twice a day at 8:00 a.m. and at 3:00 p.m.

Blood sampling

Venous blood samples were drawn just prior to MPNS, prior to the first OKT3 administration and 30, 60, 120, 180, 240, 720 and 1440 minutes afterwards. Total leukocyte and differential counts were determined by flow cytometry (Technicon H1 system, Technicon Instruments, Tarrytown, New York, USA).

After immediate centrifugation of the blood samples, plasma was stored at −70°C. In order to avoid interassay variation, all samples obtained from each single individual were thawed later on and assayed in the same experiment. Plasma TNF-α levels were determined with a commercially available ELISA (Medgenix, Billerica, Massachusetts, USA). IL-6 levels were determined by ELISA as has been described previously [22]. The lower limit of detection of the TNF assay was 5 pg/ml, and of the IL-6 assay 10 pg/ml.

Table 1. Body temperature in °C (median and 95% confidence interval) of the three groups studied at different time points after the first OKT3 administration

Time *(hours)* after OKT3 administration	−6 hr group	−1 hr group	−6/−1 hr group
0	36^{9} (36^{5}–37^{3})	37^{2} (36^{7}–37^{8})	36^{6} (36^{3}–36^{8})
2	37^{3} (36^{5}–38^{0})	38^{9} (38^{4}–39^{2})	36^{7} (35^{9}–38^{0})
4	38^{0} (37^{4}–38^{6})	38^{5} (38^{0}–39^{5})	37^{3} (36^{4}–38^{1})
8	38^{6} (37^{9}–39^{0})	38^{2} (37^{7}–39^{1})	37^{0} (36^{2}–37^{9})
12	39^{4} (38^{9}–39^{9})	37^{9} (37^{4}–38^{2})	37^{8} (36^{5}–38^{8})
24	38^{0} (37^{3}–38^{6})	37^{3} (36^{7}–38^{1})	37^{1} (36^{2}–38^{5})

Statistical analysis

Values are expressed as the median and 95% confidence interval (95% CI) of each group. Although actual values of all parameters varied considerably as reflected by the big range, the kinetics of these parameters of each individual patient of the same group were comparable. Statistical analysis was performed with the Wilcoxon signed ranks test and the Mann Whitney test as indicated in the text. A probability (P) value < 0.05 was considered to be significant.

Results

Lymphocyte counts in patients treated with 500 mg MPNS only

Lymphocyte counts decreased to 60% of pretreatment values (95% C.I. 42 to 77%) at one hour following MPNS infusion (P = 0.0431, Wilcoxon signed ranks test) and to 37% (95% C.I. 27 to 47%) at six hours following MPNS administration (P = 0.0431, Wilcoxon signed ranks test). The difference between one and six hours after administration of MPNS was not significant.

Patients treated with OKT3

Body temperature. Table 1 and Figure 1 (for clear visualization of body temperature kinetics) show the median body temperature of the three groups studied, which did not show a significant difference before OKT3 administration. In the −1 hr group body temperature reached 38^{9}°C (95% CI, 38^{4} to 39^{2}°C) at two hours after OKT3. In the −6 hr group body temperature increased to 39^{4}°C (95% CI, 38^{9} to 39^{9}°C) at 12 hours following OKT3. In the −6/−1 hr group temperature rose to a maximum of 37^{8}°C only (95% CI, 36^{5} to 38^{8}°C). Peak temperature levels were significantly decreased in the −6/−1 hr group as compared to the −6 and the −1 hr group (Mann Whitney P = 0.0459 and P = 0.0157, respectively). On the day following the second administration of OKT3 peak body temperature in the −1 hr group, −6 hr group and −6/−1 hr group were 38^{0}°C (95% CI, 37^{4} to 39^{0}°C), 38^{8}°C (95% CI, 38° to 39^{6}°C) and 38^{4}°C (95% CI, 36^{9} to 39^{4}°C), respectively. These data were statistically not different.

Side effects. Side effect scores of the three groups are depicted in Figure 2. Peak side effects score in the −1 hr group was 3.0 (95% CI, 1.8 to 4.0), in the −6 hr group 3.0 (95% CI, 1.5 to 3.4) and in the −6/−1 hr group 1.0, (95% CI 0.4 to 1.6). Peak side effects were significantly decreased in the −6/−1 hr group as compared to the −6 and −1 hr group (Mann Whitney P = 0.0392 and 0.016, respectively). All patients in the −6/−1 hr group had chills one hour after administration of OKT3, followed by a relatively uneventful period. There were no significant differences between the −6 hour and the −1 hour groups. On the day after

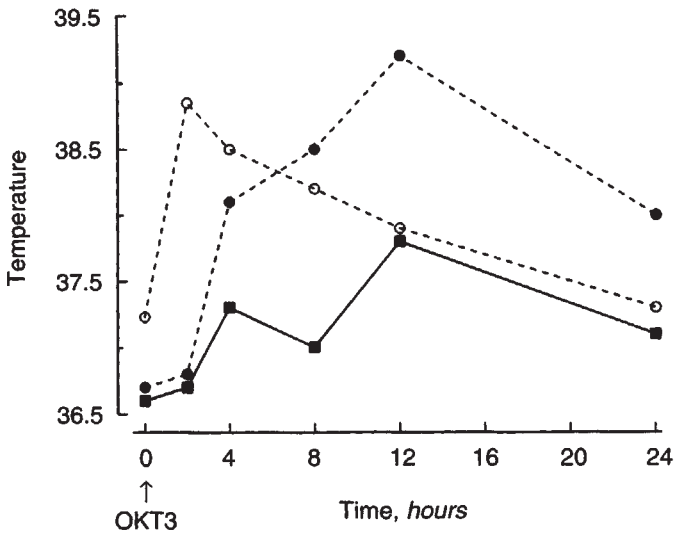

Fig. 1. *Body temperature during the first day following administration of OKT3.* Results are represented as medians in each group. Symbols are: (○) −1 hr group; (●) −6 hr group; (■) −1/−6 hr group.

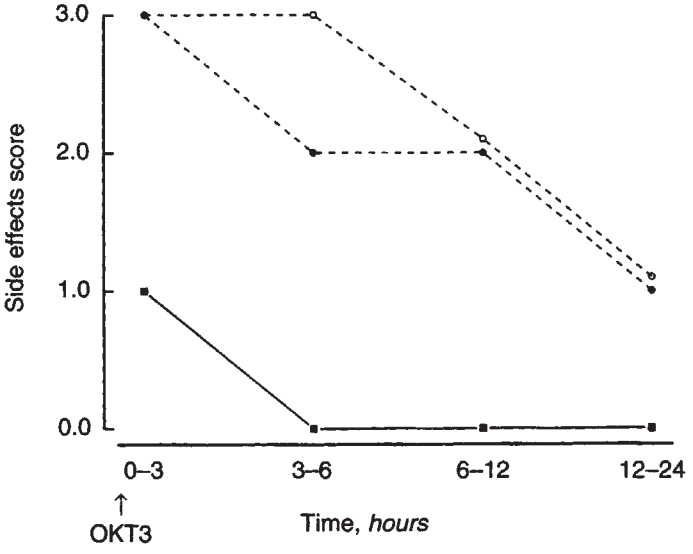

Fig. 2. *Clinical side effects score plotted against time.* Results are represented as medians in each group. Symbols are: (○) −1 hr group; (●) −6 hr group; (■) −1/−6 hr group.

the second OKT3 administration, peak side effects score in the −1 hr group, −6 hr group and −1/−6 hr group were 1 (95% CI, 0.51 to 1.71), 2 (95% CI, 0.88 to 2.2) and 1 (95% CI, 0.22 to 2.7), respectively. These differences were not significant.

Blood pressures in the three groups remained essentially unchanged, following the first and second OKT3 administration (Table 2).

Absolute lymphocyte counts. Corticosteroids reduced the absolute number of T lymphocytes in all three groups significantly from 0.79 × 10^9/liter (95% CI, 0.59 to 1.44 × 10^9/liter) before the administration of MPNS to 0.49 × 10^9/liter (95% CI, 0.42 to 0.62 × 10^9/liter) before the administration of OKT3: from 0.67 × 10^9/liter (95% CI, 0.41 to 0.94 × 10^9/liter) to 0.48 × 10^9/liter (95% CI, 0.31 to 0.73 × 10^9/liter) and from 0.71 × 10^9/liter (95% CI, 0.38 to 1.0 × 10^9/liter) to 0.34 × 10^9/liter (95% CI, 0.26 to 0.54 × 10^9/liter) in the −6 hr, −1 hr and the −6/−1 hr groups, respectively. There was no significant difference between the absolute numbers of circulating T cells of the three groups just prior to OKT3 treatment.

Table 2. Blood pressure following the first and second administration of OKT3

OKT3 administration	−6 hr group		−1 hr group		−6/−1 hr group	
	first	second	first	second	first	second
Patient						
1 7.00 am	150/100	140/100	140/70	125/70	140/85	140/85
3.00 pm	150/90	110/65	160/80	140/65	145/90	115/80
2 7.00 am	115/75	105/60	140/90	130/80	160/110	125/75
3.00 pm	110/75	110/75	115/60	115/65	125/85	120/80
3 7.00 am	130/85	130/80	140/100	150/110	140/95	130/90
3.00 pm	130/85	100/50	125/80	170/95	160/80	145/80
4 7.00 am	180/110	150/90	160/100	150/100	120/70	130/70
3.00 pm	120/75	110/90	150/95	155/100	150/80	120/80
5 7.00 am	140/80	140/80	120/100	130/70	125/80	110/70
3.00 pm	125/75	125/75	110/90	125/60	140/80	140/90
6 7.00 am	165/90	130/75	180/95	140/90	125/80	110/80
3.00 pm	140/70	130/75	160/100	160/100	115/80	105/70
7 7.00 am	170/100	140/80	140/90	140/100		
3.00 pm	160/90	160/95	135/95	95/70		
8 7.00 am	150/90	160/90	160/90	120/70		
3.00 pm	170/100	150/90	130/80	140/75		
9 7.00 am	120/90	100/70	120/80	125/80		
3.00 pm	100/70	110/70	130/80	125/80		
10 7.00 am	140/80	130/80	160/95	150/80		
3.00 pm	130/80	140/90	155/90	165/90		

IL-6 and TNF. Plasma levels of IL-6 and TNF of the three groups studied are depicted in Figure 3. Serum IL-6 levels in the −1 hr group increased to 43 pg/ml (95% CI, 7 to 230 pg/ml), in the −6 hr group to 180 pg/ml (95% CI, 5 to 4097), and in the −6/−1 hr group to 14 (95% CI, 5 to 37). Peak serum IL-6 levels were significantly decreased in the −6/−1 hr group as compared to the −6 hr group (Mann Whitney $P = 0.0152$), but not as compared to the −1 hr group (Mann Whitney $P = 0.153$). Peak IL-6 levels in both the −1 hr group and the −6/−1 hr group appeared three hours following administration of OKT3. Peak IL-6 levels in the −6 hr group appeared to be postponed for three hours. Serum TNF levels in the −1 hr group increased to 1050 pg/ml (95% CI, 755 to 1511 pg/ml), in the −6 hr group to 433 pg/ml (95% CI, 199 to 907 pg/ml) and in the −6/−1 hr group to 559 pg/ml (95% CI, 283 to 942 pg/ml). The −1 hr group experienced significantly higher TNF levels as compared to the −6 hr and the −6/−1 hr groups ($P = 0.0321$, Mann Whitney).

Discussion

Since the use of OKT3 as an immunosuppressive agent, several therapeutic interventions have been tried to reduce adverse reactions in man, among which pretreatment with indomethacin [23, 24], pentoxyfylline [25] and mAb anti-TNF [26]. In all these studies corticosteroids were also administered in different dosages ranging from 1 mg/kg to 500 mg simultaneously with, or one to two hours before the first OKT3 injection. Up to now, none of the tested approaches could totally prevent side effects complicating therapy with mAb anti-CD3.

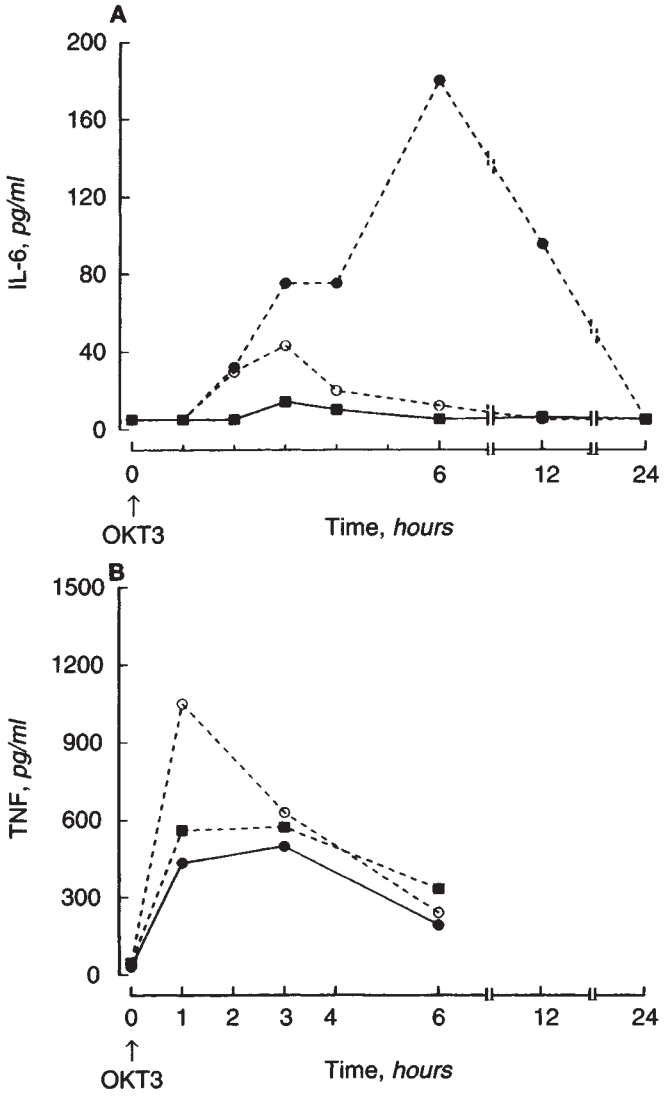

Fig. 3. *Serum Il-6 levels (A) and serum TNF levels (B) plotted against time.* Results are represented as medians in each group. Symbols are: (○) −1 hr group; (●) −6 hr group; (■) −1/−6 hr group.

Regarding pretreatment with corticosteroids, several doses and time points have been evaluated. In mice, administration of corticosteroids just prior to the administration of a hamster anti-CD3 mAb protected them from hypothermia, renal tubular necrosis and fatty infiltration of the liver and almost completely inhibited release of TNF and IL-6 [13]. However, these effects were most impressive when steroids were administered in a dosage of 50 mg/kg, three hours before the anti CD3 mAb was injected. In this study other doses and time intervals were not tested. Ferran et al reported a beneficial effect of a single dose of 1 mg hydrocortisone on hypothermia, diarrhea and release of IFN-γ, TNF and IL-6 in mice, when administered one hour before infusion of the anti-CD3 mAb compared to simultaneous administration. These authors stated that steroids, when given more than one hour prior to anti-CD3, were ineffective [14]. A randomized pilot study in renal transplant recipients receiving OKT3 prophylactically showed a greater salutary effect of 500 mg MPNS when given one hour prior to OKT3, than when MPNS and OKT3 were given concomitantly [16]. However, in that study the late clinical side effects and cytokine levels also might be affected by anesthesia, which was performed in all patients four to eight hours following OKT3 administration. Regarding the efficacy of different doses of corticosteroids, one study has been performed in renal transplant patients, treated prophylactically with OKT3 [27]. This study showed a more pronounced decrease in serum TNF and IFN-γ release, when these patients were pretreated with MPNS in a high dosage (8 mg/kg) than in a low dosage (1 mg/kg) both being administered at four hours prior to OKT3. However, they did not observe any difference neither in occurrence nor in severity of clinical side effects in either of the two groups.

In the present study we demonstrate a clear beneficial effect of corticosteroids when administered in two divided doses of each 250 mg at six hours and at one hour preceding the first dose of OKT3.

We initially hypothesized that administration of OKT3 at the nadir of circulating mononuclear blood cells would reduce clinical side effects. Previous studies have shown that oral administration of 10, 30 and 60 mg prednisolone to healthy individuals induces lymphocytopenia with a nadir at six hours after intake of prednisolone [19]. Prior to the onset of this study, we studied peripheral blood lymphocyte kinetics in five renal transplant recipients treated for acute rejection with 500 mg MPNS. One hour after the administration of MPNS, absolute counts of circulating lymphocytes were significantly decreased. Six hours following administration of MPNS lymphocyte numbers were even more decreased as compared to one hour after MPNS administration. Although this difference reached no significance, we assumed that the optimal time interval between the administration of MPNS and OKT3 would be six hours. The more so as previous data from the literature show that prednisolone affects CD4-positive lymphocytes more than CD8-positive lymphocytes, resulting in a decline of CD4/CD8 ratio maximally at six hours after administration of prednisolone [19] and since a positive correlation between $CD4^+$ cells and clinical side effects has been found [10]. In agreement with the above-described findings we found that absolute numbers of circulating lymphocytes between the three groups—although significantly decreased as compared to levels prior to administration of MPNS—did not differ significantly just before administration of OKT3.

The results of the present study do not support our initial hypothesis. We could not detect an advantage of administration of corticosteroids six hours prior to OKT3 above the administration of corticosteroids one hour prior to OKT3 regarding either plasma levels of IL-6, body temperature or side effect score. Apparently steroid-induced circulating lymphocytopenia has no major effect on adverse reactions after the first administration of OKT3. This may be explained by the fact that steroids probably induce margination of circulating lymphocytes but have no influence on the total body lymphocyte burden [28]. Circulating lymphocytes numbers after the administration of MPNS may not be representative of total body lymphocyte counts, whereas in a "steady state"—as in the patient groups studied by Gaston et al—they may.

However, because of the observations in both groups (−6 hr; −1 hr) we could indeed demonstrate an additive beneficial effect on

all parameters of administration of corticosteroids in two divided doses at −6 and −1 hr, respectively.

Obviously, mechanisms other than a reduced absolute peripheral lymphocyte count have a role. Explanations for the observed findings may be deduced from data obtained from experiments both *in vitro* [29–33] and *in vivo* [34]. Corticosteroids are known to inhibit the production of TNF by LPS-stimulated human monocytes in a dose and time dependent manner; maximum inhibition was achieved when monocytes were preincubated with corticosteroids during 48 hours. Less inhibition was observed when incubation time was shortened [29]. Others demonstrated inhibition of the transcription and translation of mRNA for TNF by dexamethasone [30]. Moreover, incubation of a myelomonocytic cell line (U937) with corticosteroids during 48 hours reduced transcription of mRNA of FcRI and FcRII and decreased surface expression of FcγR [31]. These receptors have a role in activation of monocytes and consequently in the triggering of release of TNF and IL-6 [32]. Hydrocortisone also inhibits IL-6 synthesis by LPS-stimulated human peripheral blood mononuclear cells [33].

In our study, decreased TNF peak levels after OKT3 administration correlated well with an abrogated pyrogen response in the first few hours following OKT3, but less with other clinical side effects. This suggests that at least other mediators of the cytokine network or other mechanisms, such as activation of neutrophilic granulocytes, play a role in the generation of adverse reactions [12].

The decreased plasma TNF level in the −6 hr group compared to that in the −1 hr group is in agreement with results of others [34], who found lower TNF levels and unchanged IL-6 levels following LPS infusion in human volunteers, providing LPS infusion was preceded by corticosteroids administered by continuous infusion during six hours. When steroid infusion was followed by an interval of six hours prior to LPS, there was no difference between clinical side effects compared to the group who received LPS alone, but TNF levels remained decreased and IL-6 levels even increased.

Our patients in the −6 hr group had peak IL-6 levels after 6 hours, and peak body temperature 12 hours after administration of OKT3. Indeed, a delay of four hours between IL-6 administration and a systemic reaction has been reported [35].

We realize that patients in our study were not randomly assigned to the different groups and that this easily can introduce bias, especially regarding clinical side effects. However, we think that we still may draw conclusions from our findings since the other parameters (body temperature, serum TNF and IL-6 levels) support the data concerning the adverse reactions. Body temperature and cytokine levels are not liable to bias.

Despite pretreatment with steroids, first dose effects were still seen. Alternate approaches or additional treatment such as administration of anti-TNF or anti-IFNγ mAbs may be of supplementary value in reducing adverse reactions after OKT3 [36, 37].

We conclude that two doses of 250 mg MPNS administered six hours and one hour before the first administration of OKT3 effectively, although not completely, prevents clinical side effects. This regimen is superior to administration of the same amount of steroids in one dose either one hour or six hours before the administration of OKT3. Beneficial effects of divided steroid administration on clinical side effects were mainly apparent on the first day following OKT3 administration.

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References

1. Ortho Multicenter Transplant Group: A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. Ortho Multicenter Transplant Study Group. *N Engl J Med* 313:337–342, 1985
2. Thisthlethwaite JR, Cosimi AB, Delmonico FL, Rubin RH, Talkoff-Rubin N, Nelson PW, Fang L, Russell PS: Evolving use of OKT3 monoclonal antibody for treatment of renal allograft rejection. *Transplantation* 38:695–701, 1984
3. Deierhoi MH, Barber WH, Curtis JJ, Julian B, Luke RG, Hudson S, Barger BO, Diethelm AG: A comparison of OKT3 monoclonal antibody and corticosteroids in the treatment of acute renal allograft rejection. *Am J Kidney Dis* 11:86–89, 1988
4. Norman DJ, Shield CF, Barry J, Bennett WM, Henell K, Kimball J, Funnell B, Hubert B: Early use of OKT3 monoclonal antibody in renal transplantation to prevent rejection. *Am J Kidney Dis* 11:107–110, 1988
5. Thisthlethwaite JR, Stuart JK, Mayes JT, Gaber AO, Woodle S, Buckingham MR, Stuart FP: Monitoring and complications of monoclonal therapy. *Am J Kidney Dis* 11:112–119, 1988
6. Chatenoud L, Ferran C, Reuter A, Legendre C, Gevaert Y, Kreis H, Franchimont P, Bach J: Systemic reaction to the anti-T-cell monoclonal antibody OKT3 in relation to serum levels of tumor necrosis factor and interferon-gamma. *N Engl J Med* 320:1420–1421, 1989
7. Ferran C, Sheehan K, Dy M, Merite S, Schreiber R, Merite S, Landais P, Noel L, Grau G, Bluestone J, Bach J, Chatenoud L: Cytokine-related syndrome following injection of anti-CD3 monoclonal antibody: further evidence for transient in vivo T cell activation. *Eur J Immunol* 20:509–515, 1990
8. Abramowicz D, Schandene L, Goldman M, Crusiaux A, Vereerstraeten P, De Pauw L, Wybran J, Kinnaert P, Dupont E, Toussaint C: Release of tumor necrosis factor, interleukin-2, and gamma-interferon in serum after injection of OKT3 monoclonal antibody in kidney transplant recipients. *Transplantation* 47:606–608, 1989
9. Chatenoud L, Ferran C, Legendre C, Thouard I, Merite S, Reuter A, Gevaert Y, Kreis H, Franchimont P, Bach J: In vivo cell activation following OKT3 administration. Systemic cytokine release and modulation by corticosteroids. *Transplantation* 49:697–702, 1990
10. Gastron RS, Deierhoi MH, Patterson T, Prasthofer E, Julian BA, Barber WH, Laskow DA, Diethelm AG, Curtis JJ: OKT3 first-dose reaction: Association with T cell subsets and cytokine release. *Kidney Int* 39:141–148, 1991
11. Bloemena E, Ten Berge RJM, Surachno S, Wilmink JM: Kinetics of interleukin 6 during OKT3 treatment in renal allograft recipients. *Transplantation* 50:330–331, 1990
12. Raasveld MHM, Bemelman FJ, Schellekens PTA, Hack CE, Ten Berge RJM: Complement activation during OKT3 treatment: A possible explanation for respiratory side effects. *Kidney Int* 43:1140–1149, 1993
13. Alegre ML, Vandenabeele P, Depierreux M, Florquin S, Deschodt-Lanckman M, Flamand V, Moser M, Oberdan L, Urbain J, Fiers W, Goldman M: Cytokine release syndrome induced by the 145-2c11 anti-CD3 monoclonal antibody in mice: Prevention by high doses of methylprednisolone. *J Immunol* 146:1184–1187, 1991
14. Ferran C, Dy M, Merite S, Sheehan K, Schreiber R, Leboulenger F, Landais P, Bluestone J, Bach J, Chatenoud L: Reduction of morbidity and cytokine release in anti-CD3 moab-treated mice by corticosteroids. *Transplantation* 50:642–648, 1990

15. PECES R, URRA JM, ESCALADA P, GOROSTIDI M, GONZALES E, LOPEZ-L-ARREO C: High-dose methylprednisolone inhibits the OKT3-induced cytokine related syndrome. *Nephron* 63:118–118, 1993
16. CHATENOUD L, LEGENDRE C, FERRAN C, BACH J-F, KREIS H: Corticosteroid inhibition of the OKT3-induced cytokine-related syndrome—Dosage and kinetics prerequisites. *Transplantation* 51:334–338, 1991
17. FAUCI AS, DALE DC: The effect of hydrocortisone on the kinetics of normal human lymphocytes. *Blood* 46:235–243, 1975
18. OOSTERHUIS B, TEN BERGE RJM, SCHELLEKENS PTHA, VAN BOXTEL CJ: Concentration-dependent effects of prednisolone on lymphocyte subsets and mixed lymphocyte culture in humans. *J Pharm Exp Ther* 243:716–722, 1987
19. TEN BERGE RJM, SAUERWEIN HP, YONG SL, SCHELLEKENS PTHA: Administration of prednisolone *in vivo* affects ratio of OKT4/OKT8 and the LDH-isoenzyme pattern of human T lymphocytes. *Clin Immunol Immunopathol* 30:91–103, 1984
20. ROTA S, RAMBALDI A, GASPARI F, NORIS M, DAINA E, BENIGNI A, PERNA A, DONADELLI R, REMUZZI G, GARATTINI: Methylprednisolone dosage effects on peripheral subpopulation and eicosanoid synthesis. *Kidney Int* 42:981–990, 1992
21. CLAMAN H: Corticosteroids and lymphoid cells. *N Engl J Med* 287:388–397, 1972
22. HELLE M, BOEYE L, GROOT DE E, VOS DE A, AARDEN LA: Sensitive ELISA for interleukin-6; detection of IL-6 in biological fluids: synovial fluids and sera. *J Immunol Methods* 138:47–52, 1991
23. SHIELD CF, KAHANA L, PIRSCH J, VERGNE-MARINI P, FIRST MR, SCHROEDER TJ, COHEN D, NORMAN DJ, MONACO A, MARTINEZ A, DINARELLO CA, DEHLINGER J, WU SH, VAN HORN A: Use of indomethacin to minimize the adverse reactions associated with orthoclone OKT3 treatment of kidney allograft rejection. *Transplantation* 54:164–165, 1992
24. CHAN GL, WEINSTEIN SS, WRIGHT CE, BOWERS VD, ALVERANGA DY, SHIRES DL, ACKERMANN JR, LEFOR W, KAHANA L: Encephalopathy associated with OKT3 administration; possible interaction with indomethacin. *Transplantation* 52:148–150, 1991
25. ALEGRE ML, GASTALDELLO K, ABRAMOWICZ D, KINNAERT P, VEREER-STRAETEN P, DE PAUW L, VANDENBEELE P, MOSER M, OBERDAN L, GOLDMAN M: Evidence that pentoxifylline reduces anti-CD3 monoclonal antibody-induced cytokine release syndrome. *Transplantation* 52:674–679, 1991
26. CHARPENTIER B, HIESSE C, LANTZ O, FERRAN C, STEPHENS S, O'SHAUGNESSY D, BODMER M, BENOIT G, BACH J, CHATENOUD L: Evidence that antihuman tumor necrosis factor monoclonal antibody prevents OKT3-induced acute syndrome. *Transplantation* 54:997–1002, 1992
27. GOLDMAN M, ABRAMOWICZ D, DE PAUW L, ALEGRE M, WIDERA I, VEREERSTRAETEN P, KINNAERT P: OKT3-induced cytokine release attenuation by high-dose methylprednisolone letter. *Lancet* 2:802–803, 1989
28. FAUCI AS, DALE DC: The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. *J Clin Invest* 53:240–246, 1974
29. WAAGE A, BAKKE O: Glucocorticoids suppress the production of tumour necrosis factor by lipopolysaccharide-stimulated human monocytes. *Immunol* 63:299–302, 1988
30. BEUTLER B, KROCHIN N, MILSARK IW, LUEDKE C, CERAMI A: Control of cachectin (tumor necrosis factor) synthesis: Mechanism of endotoxin resistance. *Science* 232:977–980, 1986
31. GRATTAGE LP, MCKENZIE IFC, HOGARTH PM: Effects of PMA, cytokines and dexamethasone on the expression of cell surface Fc receptors and mRNA in U937 cells. *Immunol Cell Biol* 70:97–105, 1992
32. DUITS AJ, AARDEN LA, ERNST LK, CAPEL PJA, VAN DE WINKEL JGJ: Isotype-specific cross-linking of select human FcgammaR isoforms triggers release of IL-6. *Clin Exp Immunol* 92:225–231, 1993
33. HIROOKA Y, MITSUMA T, NOGIMORI T, ISHIZUKI Y: Effect of hydrocortisone on interleukin-6 production in human peripheral blood mononuclear cells. *Mediators Inflam* 1:9–13, 1992
34. BARBER AE, COYLE SM, MARANO MA, FISCHER E, CALVANO SE, FONG Y, MOLDAWER LL, LOWRY SF: Glucocorticoid therapy alters hormonal and cytokine responses to endotoxin in man. *J Immunol* 150:1999–2006, 1993
35. WEBER J, YANG JC, TOPALIAN SL, PARKINSON DR, SCHWARTZENTRUBER DS, ETTINGHAUSEN SE, GUNN H, MIXON A, KIM H, COLE D, LEVIN R, ROSENBERG SA: Phase I trial of subcutaneous interleukin-6 in patients with advanced malignancies. *J Clin Oncol* 11:499–506, 1993
36. CHARPENTIER B, HIESSE C, LANTZ O, FERRAN C, STEPHENS S, O'SHOUGNESSY D, BODMER JF, CHATENOUD L: Evidence that antihuman tumor necrosis factor monoclonal antibody prevents OKT3-induced acute syndrome. *Transplantation* 54:997–1002, 1992
37. MATTHYS P, DILLEN C, PROOST P, HEREMANS H, VAN DAMME J, BILLIAU A: Modification of the anti-CD3-induced cytokine release syndrome by anti-interferon-gamma or anti-interleukin-6 antibody treatment: protective effects and biphasic changes in blood cytokine levels. *Eur J Immunol* 23:2209–2216, 1993